

UPDATES IN THE EARLY MANAGEMENT OF ACUTE ISCHEMIC STROKE

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Learning Objectives

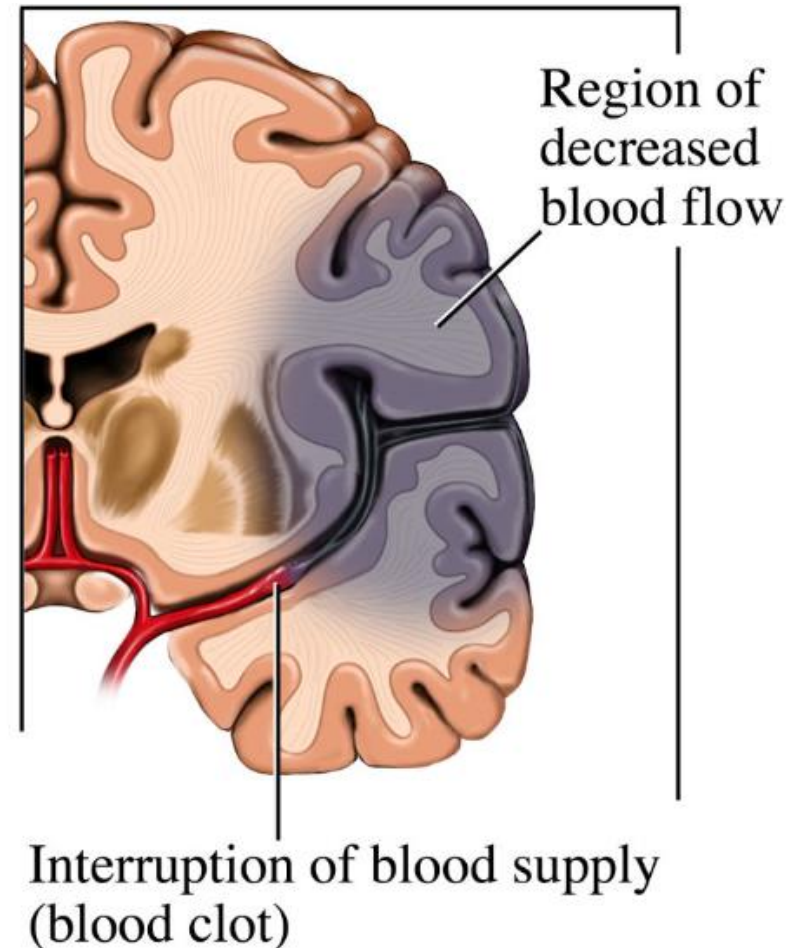
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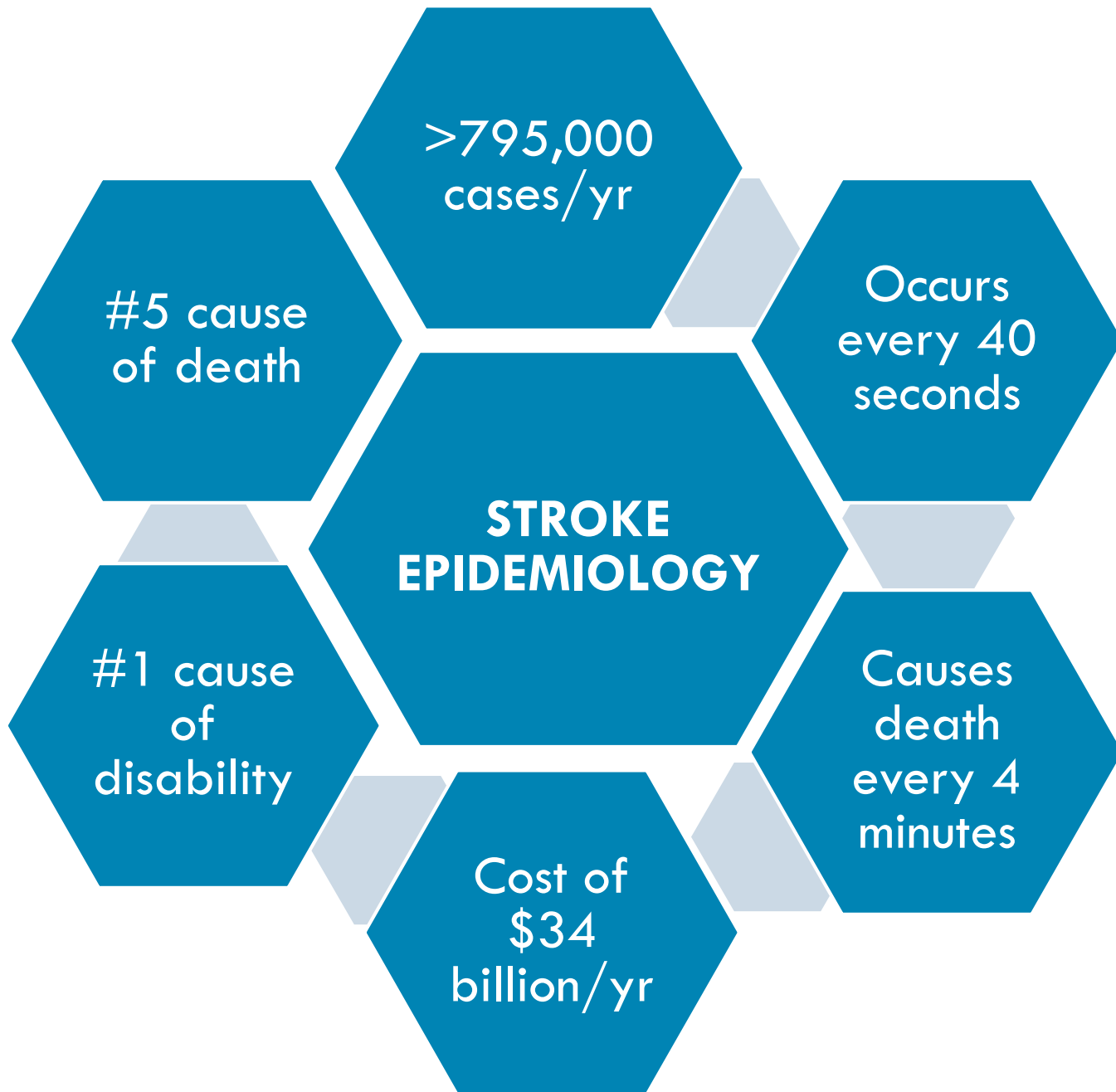
- Provide recommendations for initial assessment of patients presenting with acute ischemic stroke (AIS)
- Identify the indications and contraindications for IV alteplase
- Determine whether a patient with AIS is a candidate for alteplase therapy
- Manage blood pressure in a patient presenting with AIS
- Evaluate the literature on blood pressure management in AIS
- Describe the role of antiplatelet agents and anticoagulants in the treatment of AIS
- Examine the literature on use of dual antiplatelet therapy for early secondary stroke prevention

Ischemic Stroke Overview

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- Sudden onset of a focal neurologic deficit
- Persists for ≥ 24 hours
- Results from cerebral artery occlusion due to thrombus/embolism
- Commonly due to atherosclerosis
- Account for 87% of strokes





2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

*Reviewed for evidence-based integrity and endorsed by the American Association of Neurological
Surgeons and Congress of Neurological Surgeons*

Endorsed by the Society for Academic Emergency Medicine and Neurocritical Care Society

*The American Academy of Neurology affirms the value of this guideline
as an educational tool for neurologists.*

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ACC/AHA Class of Recommendations

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Class	Phrases Used in Guidelines	Risk vs. Benefit
I (Strong)	<ul style="list-style-type: none">• Is recommended• Is indicated/beneficial	Benefit >>> Risk
IIa (Moderate)	<ul style="list-style-type: none">• Is reasonable• Can be useful/effective	Benefit >> Risk
IIb (Weak)	<ul style="list-style-type: none">• May/might be reasonable• May/might be considered	Benefit ≥ Risk
III: No Benefit (Moderate)	<ul style="list-style-type: none">• Is not recommended• Is not indicated/useful	Benefit = Risk
III: Harm (Strong)	<ul style="list-style-type: none">• Potentially harmful• Causes harm	Risk > Benefit

ACC/AHA Level of Evidence

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Level	Evidence
A	<ul style="list-style-type: none">• High quality evidence from more than 1 RCT• Meta-analyses of high quality RCTs
B-R (Randomized)	<ul style="list-style-type: none">• Moderate quality evidence from one or more RCT• Meta-analyses of moderate-quality RCTs
B-NR (Nonrandomized)	<ul style="list-style-type: none">• Moderate quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
C-LD (Limited Data)	<ul style="list-style-type: none">• Randomized or nonrandomized observational or registry studies with limitations of design or execution
C-EO (Expert Opinion)	<ul style="list-style-type: none">• Consensus of expert opinion based on clinical experience

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Initial Emergency Department Management

Stroke Severity Scale Assessment

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- Use of a stroke severity scale is recommended
- Preferred: National Institutes of Health Stroke Scale (NIHSS)
 - ▣ Score range: 0 – 42
 - ▣ Higher score indicates poorer prognosis
 - ▣ Evaluates clinical status based on many criteria including:
 - Level of consciousness
 - Motor functions in arms and legs
 - Response to commands

Brain Imaging Recommendations

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- Brain imaging recommended upon arrival to ED
- Noncontrast CT most commonly used
- Effective at identifying acute ICH
- Used in diagnosis of AIS if patient has:
 - Clinical presentation + negative noncontrast CT or noncontrast CT showing early ischemic changes
- Timing:
 - Conduct within 20 minutes of arrival
 - Target: >50% of candidates for alteplase/thrombectomy

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IV Alteplase

IV Alteplase Overview

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Category	Characteristics
Drug Class:	Thrombolytic Agent
MOA	Binds to fibrin in a thrombus → converts entrapped plasminogen to plasmin → results in local fibrinolysis
Labeled Indications	AIS – ASAP but within 3 hours of symptom onset Pulmonary Embolism – acute massive PE ST-elevation myocardial infarction
Off-Label	AIS – 3 to 4.5 hours after symptom onset
Dosing in AIS	<ul style="list-style-type: none">• 0.9 mg/kg; max 90 mg• Give 10% as bolus over 1 minute• Remaining 90% is infused over 60 minutes
Key Adverse Events	<ul style="list-style-type: none">• BLEEDING – e.g. ICH (>10%); GI & GU bleed (4-5%)• Angioedema

Hospital Door-to-Needle Time (DTN) Goals

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- Primary Goal (Recommended):
 - DTN time <60 minutes for $\geq 50\%$ of patients receiving IV alteplase
 - Revised recommendation (COR: I; LOE: B-NR)
- Secondary Goal (Reasonable):
 - DTN time <45 minutes in $\geq 50\%$ of patients receiving IV alteplase
 - New recommendation (COR: IIb; LOE: C-EO)

IV Alteplase Administration

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- Measure BP and perform neurologic assessments
 - ▣ First 2 hours: every 15 minutes
 - ▣ Next 6 hours: every 30 minutes
 - ▣ Next 16 hours: every hour
 - ▣ Increase frequency and treat if BP >180/105 mm Hg
- Discontinue and obtain emergency head CT if...
 - ▣ Severe headache
 - ▣ Acute hypertension
 - ▣ Nausea or vomiting
 - ▣ Worsening neurologic exam
- Obtain follow up CT/MRI at 24 hours before starting anticoagulants or antiplatelets

IV Alteplase: Who is a Candidate?

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Within 3 Hours of Symptom Onset

- Age:
 - ▣ Equally recommended in adults <80 or >80 y/o
 - COR: I, LOE: A
- Severity:
 - ▣ Severe stroke symptoms
 - COR: I, LOE: A
 - ▣ Mild, disabling stroke symptoms
 - COR: I, LOE: B-R
 - ▣ Mild, nondisabling stroke symptoms → may be considered
 - COR: IIb, LOE: C-LD

IV Alteplase: Who is a Candidate?

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Within 3 - 4.5 Hours of Symptom Onset

- Less evidence BUT still recommended:
 - ▣ Age > 80 y
 - ▣ History of DM + prior stroke
 - ▣ Warfarin use but with INR \leq 1.7
 - ▣ Very severe stroke (NIHSS >25)
 - Benefit is uncertain (IIb)

IV Alteplase: Who is a Candidate?

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□ **Blood Glucose**

- Must be >50 mg/dL and <400 mg/dL
- MUST be measured prior to alteplase administration

□ **Blood Pressure**

- Must be $<185/110$ mm Hg

□ **Antiplatelet Use**

- Alteplase benefits outweigh increased risk of bleeding
- Monotherapy → possible small increased risk of sICH
- DUAT → probable increased risk of sICH

IV Alteplase: Who is a Candidate?

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- Menstruating women without history of menorrhagia
- Pregnant women if benefit outweighs risk
- Sickle cell disease
- Illicit drug use-associated AIS
- Seizure at onset
 - If residual impairment appears to be due to stroke
- End Stage Renal Disease
 - Normal PTT: IV alteplase is recommended
 - Elevated PTT: may have elevated risk for bleeding

IV Alteplase Contraindications

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- Time last known to be at baseline is >3 or 4.5 hours
 - ▣ Unknown time of stroke onset
 - ▣ Patient awoke with stroke >3 or 4.5 hours from last known time at baseline
- CT scan reveals acute intracranial hemorrhage
- Severe hypoattenuation on CT brain imaging
- Severe head trauma in past 3 months
- Symptoms consistent with infective endocarditis

IV Alteplase Contraindications

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- GI bleed within 21 days
- Structural GI malignancy
- History of intracranial hemorrhage
- Prior ischemic stroke within 3 months
- Intracranial/spinal surgery within prior 3 months
- AIS suspected to be associated with aortic arch dissection
- Presence of intra-axial intracranial neoplasm

IV Alteplase Contraindications

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- Coagulopathy (ANY of the following):
 - ▣ Platelets $<100,000/\text{mm}^3$
 - ▣ INR >1.7
 - ▣ aPTT >40 s
 - ▣ PT >15 s
 - ▣ Avoid due to unknown safety and efficacy (COR: III: Harm; LOE C-EO)
- Do NOT delay alteplase for coagulation panel if it is expected to be normal

IV Alteplase in Patients with Anticoagulant Use

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LMWH

- Contraindicated if treatment dose given in past 24 hours

Thrombin & Factor Xa Inhibitors

- Contraindicated in most cases
- May use alteplase ONLY if one of the following:
 - Normal lab test (e.g. aPTT, INR, platelet count, ecarin clotting time, thrombin time, or direct factor Xa activity assay)
 - Anticoagulant not used for >48 hours in patient with normal renal function

Which of the following is a contraindication to IV alteplase in a patient presenting with AIS?

- A. Recent use of aspirin
- B. Recent use of aspirin + clopidogrel
- C. Recent use of enoxaparin for DVT prophylaxis
- D. Warfarin use (INR 1.8)
- E. Use of rivaroxaban 36 hours ago (all coagulation tests within normal limits)

Patient Case

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- HPI: Mr. Rogers is an 82 year old male who woke up at 7 am with slurred speech and left sided facial droop and weakness. He did not exhibit any signs and symptoms when he went to sleep the night before at 11 pm. His CT scan shows early ischemic changes and his NIHSS score is 20.
- PMH: Type 2 DM, HTN
- Medications:
 - ▣ Aspirin 81 mg PO QAM
 - ▣ Insulin glargine 20 units SQ QHS
 - ▣ Novolog 5 units SQ TID-AC
 - ▣ Amlodipine 10 mg PO QAM
 - ▣ Atorvastatin 20 mg PO QHS
- Vitals: BP 200/100 mm Hg; HR 90 bpm; RR 14 breaths/min

Which of the following lab tests **MUST** be available prior to considering use of IV alteplase in this patient?

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- A. INR
- B. Platelet count
- C. WBC
- D. Blood glucose
- E. aPTT

Is Mr. Rogers a candidate for IV alteplase therapy?

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- A. No – Mr. Rogers cannot receive IV alteplase because he missed the recommended time window
- B. No – Mr. Rogers cannot receive IV alteplase because is older than age 80
- C. No – Mr. Rogers cannot receive IV alteplase because his heart rate is >80 bpm
- D. Yes – Mr. Rogers can receive IV alteplase if his BP is lowered to $<185/110$ mm Hg

Blood Pressure Management in AIS

HOW LOW/HIGH SHOULD WE GO?



Guideline Recommendation

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Recommendation	COR	LOE
<ul style="list-style-type: none">• Correct hypotension and hypovolemia• Goal:<ul style="list-style-type: none">• Maintain systemic perfusion levels to support organ function<p>(new recommendation)</p>	I	C-EO
<p><u>RATIONALE:</u></p> <ul style="list-style-type: none">• Optimal BP to maintain unknown• Some observational studies show worse outcomes with low BPs		

Guideline Recommendations Continued

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Recommendation	COR	LOE
Before administering IV alteplase lower... Systolic BP to <185 mm Hg Diastolic BP to <110 mm Hg (reworded recommendation)	I	B-NR
Before mechanical thrombectomy lower... Systolic BP to < 185/mm Hg Diastolic BP to < 110 mm Hg (reworded recommendation)	IIa	B-R

Guideline Rationale for BP Targets

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- RCTs excluded patients with BP $>185/110$ mm Hg
- Increased risk of hemorrhage observed with IV alteplase in patients with...
 - ▣ Higher BPs
 - ▣ Greater BP variability
- Optimal BP target unknown
- Reasonable to target BPs used in RCTs

Managing BP Pre- and Post- Alteplase Therapy

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Before Alteplase Administration

- Recommended Agents
 - ▣ Labetalol
 - ▣ Nicardipine
 - ▣ Clevidipine
 - ▣ May consider other drugs (e.g. hydralazine, enalaprilat)
- **Do NOT give alteplase if BP <185/110 mm Hg not maintained**

After Alteplase Administration

- Recommended agents:
 - ▣ Labetalol
 - ▣ Nicardipine
 - ▣ Clevidipine
- If BP not controlled or DBP >140 mm Hg consider IV sodium nitroprusside

BP Management

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Case	Recommendation	COR, LOE
BP lowering required by comorbid conditions <ul style="list-style-type: none"> • Acute heart failure • Acute coronary event 	<ul style="list-style-type: none"> • Early lowering of BP by 15% probably safe 	I, C- EO (new)
BP \geq220/120 mm Hg <ul style="list-style-type: none"> • No alteplase/thrombectomy • No comorbidities 	<ul style="list-style-type: none"> • Benefit of lowering BP uncertain • Reasonable to \downarrow BP by 15% in first 24 hours 	IIb, C-EO (new)
BP $<$220/120 mm Hg <ul style="list-style-type: none"> • No alteplase/thrombectomy • No comorbidities 	<ul style="list-style-type: none"> • Treating HTN within first 48-72 not effective at preventing death or dependency 	III: No benefit, A (revised)

Guideline Rationale for Recommendations

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- Excessive BP lowering worsens cerebral ischemia
- Acute comorbidities may require urgent BP reduction
- Multiple RCTs show starting BP meds after AIS can be safe but lacks benefit
- Limited data regarding:
 - ▣ Patients with extreme HTN
 - ▣ BP management within first 6 hours after stroke
 - ▣ Patients with coexistent indications for acute BP reduction

Supporting Evidence: Vemmos et al.

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- Objective:
 - ▣ Evaluate relationship between SBP/DBP on admission and early/late mortality in stroke
- Design:
 - ▣ Prospective study of hospitalized first-time stroke patients
- Subjects:
 - ▣ 1,121 patients admitted within 24h of stroke onset and followed for 12 months

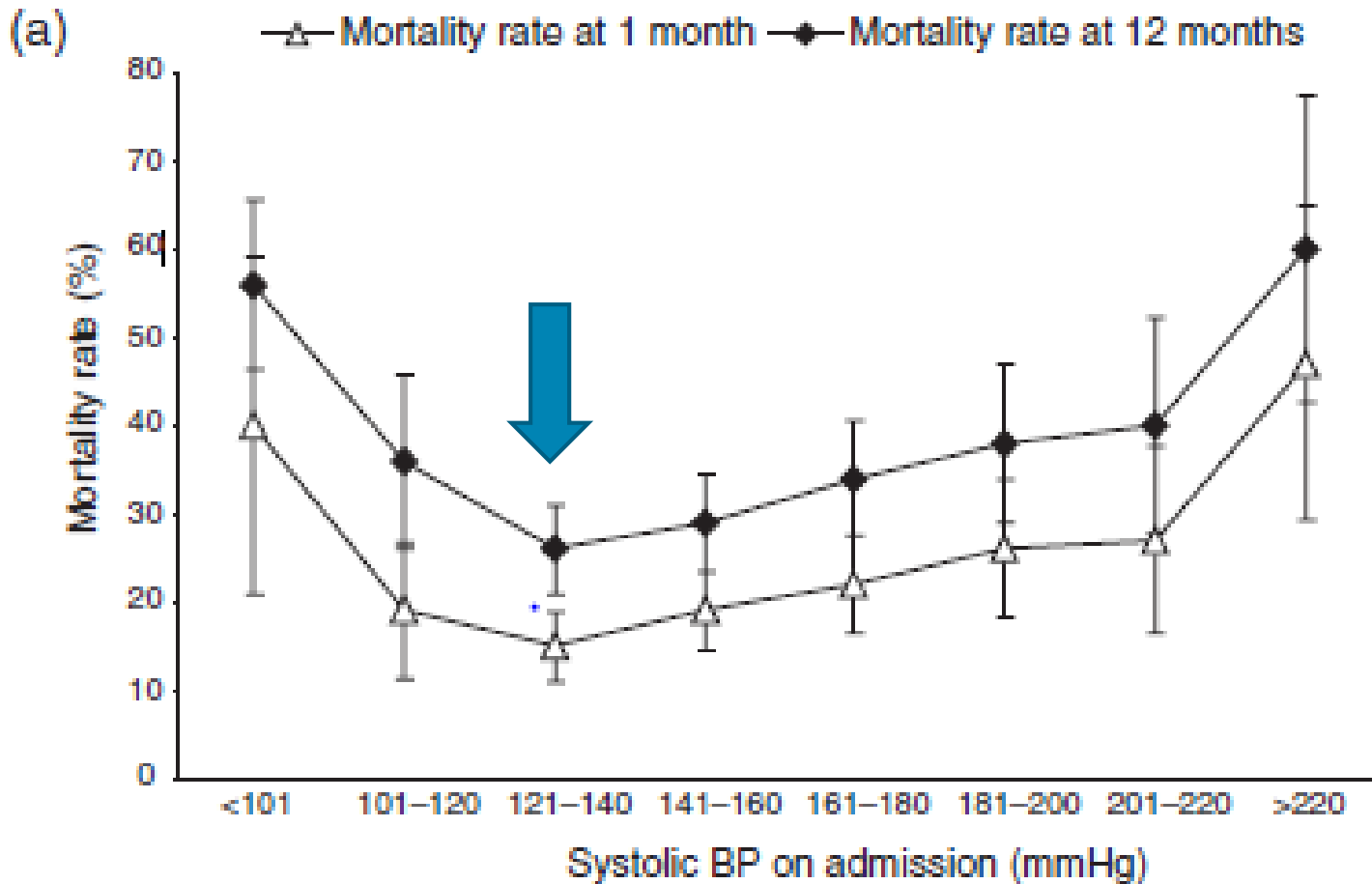
Vemmos et al. Continued

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- Primary Outcome:
 - ▣ Mortality at 1 and 12 months after stroke
- Results:
 - ▣ Early and late mortality in relation to admission SBP/DBP followed a 'U-curve pattern'
 - ▣ High OR low B above U-point on curve resulted in increased early and late mortality
- Best outcomes:
 - ▣ SBP 130 mm Hg
 - ▣ DBP 81 – 90 mm Hg
 - ▣ Avoid very high or low BP

Vemmos et al. Results

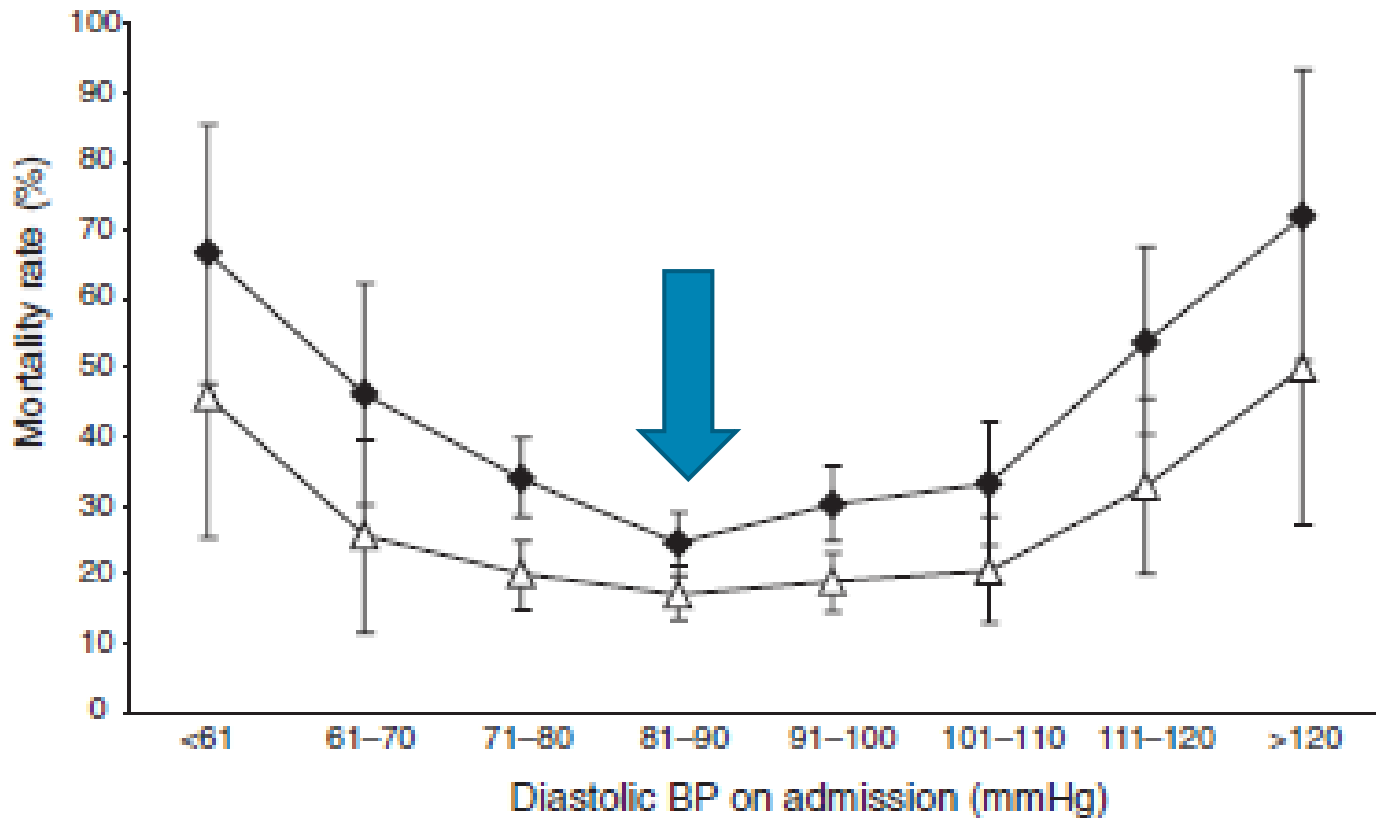
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Vemmos et al. Results Continued

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(b)



Guideline Recommendations Continued

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Recommendation	COR	LOE
<p>Treating HTN during hospitalization:</p> <ul style="list-style-type: none">• In patients with BP > 140/90 mm Hg• If neurologically stable• Safe and reasonable unless contraindicated• Goal: help with long-term BP control unless contraindicated (New recommendation)	IIa	B-R
<p><u>RATIONALE:</u></p> <ul style="list-style-type: none">• COSSACS Trial & CATIS Trial• Improved BP control after discharge when medications were restarted in hospital• No change in death or disability observed in either study		

Powers WJ, et al. *Stroke*. 2018;49:e46–e99

Robinson TG, et al. *Lancet Neurol*. 2010;9:767-775.

He J, et al. *JAMA*. 2014;311:479-489.

Ms. Park is a 66 year old female hospitalized for AIS. Her PMH includes hypertension. She has been in the hospital for a few days and is neurologically stable. Her BP today is 160/95 mm Hg. May antihypertensives be started for Ms. Park?

- A. No – Antihypertensives should not be started unless her BP increases above 220/120 mm Hg
- B. No – Antihypertensives should not be started unless her BP is $>185/110$ mm Hg
- C. No - Antihypertensives should never be started in a patient hospitalized for AIS
- D. Yes – It is safe to restart antihypertensives

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Antiplatelet Therapy in AIS

Antiplatelet Recommendations

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Recommendation	COR & LOE
<ul style="list-style-type: none">Administer aspirin within 24-48 hours of AIS onset	I, A
If IV alteplase is used: <ul style="list-style-type: none">Aspirin is delayed until 24 hours after alteplaseMay consider sooner if...<ul style="list-style-type: none">If concomitant conditions are presentBenefit considered to outweigh risk	I, A IIb, B-NR
<ul style="list-style-type: none">Do NOT use aspirin as a substitute for alteplase or mechanical thrombectomy	III, B-R
<ul style="list-style-type: none">GPIIb/IIIa receptor antagonists are not recommended for stroke management	IIb – B-R III- B-R

Aspirin Recommendations

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- Initial Dose:
 - ▣ Previous guideline: 325 mg recommended
 - ▣ Current guidelines:
 - No specific dose recommended
 - Studies showed aspirin safety and benefit at 160 - 300 mg
- If patient unable to take PO aspirin:
 - ▣ Give via rectal/nasogastric route

Mono vs. Dual Antiplatelet Therapy

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Recommendation	LOE & COR
<p><u>In patients with minor AIS:</u></p> <ul style="list-style-type: none">• DUAT (clopidogrel + aspirin) for 21 days may be beneficial for early secondary stroke prevention• Start within 24 hours• Continue for 21 days• Benefit observed for up to 90 days from AIS• Goal: Reduction of early secondary ischemic stroke:<ul style="list-style-type: none">• Risk of 3-15% in first 90 days• New recommendation based on CHANCE trial• POINT trial ongoing at time of guideline publication	IIa, B-R

Mono vs. Dual Antiplatelet Therapy

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□ CHANCE Trial:

- Clopidogrel in High Risk Patients with Acute Nondisabling Cerebrovascular Events

- Conducted at 114 centers in China

□ POINT Trial:

- Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke Trial

- Conducted at 269 sites in 10 countries (82.8% in US)

- Ongoing at time of guideline publication

Wang Y, et al. *N Engl J Med* 2013;369:11-19.

Johnston SC, et al. *N Engl J Med* 2018;379:215-25.

Mono vs. Dual Antiplatelet Therapy: CHANCE Trial

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□ **Background:**

- ▣ Aspirin (A) vs. aspirin + clopidogrel (A + C) for secondary stroke prevention

□ **Methods:**

- ▣ Randomized, double-blind, placebo controlled trial
- ▣ 5,170 patients within 24 hours of minor AIS or high-risk TIA
 - Minor AIS – NIHSS ≤ 3
 - High-risk TIA – score of 4 or greater on ABCD
- ▣ Intervention:
 - Aspirin 75 mg + placebo X 90 days
 - Clopidogrel 300 mg X 1 then 75 mg X 90 days + aspirin 75 mg X 21 days

Mono vs. Dual Antiplatelet Therapy: CHANCE Trial

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□ **Results:**

□ Stroke occurrence at 90 days:

- A + C: 8.2%
- A: 11.7%
- HR: 0.68; 95% CI 0.57-0.81; $p < 0.001$

□ Moderate or severe hemorrhage:

- A + C: 0.3% (7 events)
- A: 0.3% (8 events)
- $P = 0.73$

□ **Conclusion:**

- A+C is superior to A after minor stroke/TIA without increased risk for hemorrhage

1-Year Follow Up of CHANCE Trial

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□ **Outcomes:**

- ▣ Primary Efficacy Outcome: Ischemic or hemorrhagic stroke
- ▣ Primary Safety Outcome: Moderate-to-severe bleeding events

□ **Results:**

▣ Primary Efficacy Outcome:

- A + C: 10.6% (275 patients) vs. A: 14% (362 patients)
- HR 0.78; 95% CI, 0.65-0.93; P=0.006

▣ Safety Outcome:

- A + C: 0.3% (7 patients) vs. A: 0.4% (9 patients)
- P = 0.44

□ **Conclusion:**

- ▣ Benefit of clopidogrel + aspirin persisted for 1 year of follow up

POINT Trial

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□ **Study Population:**

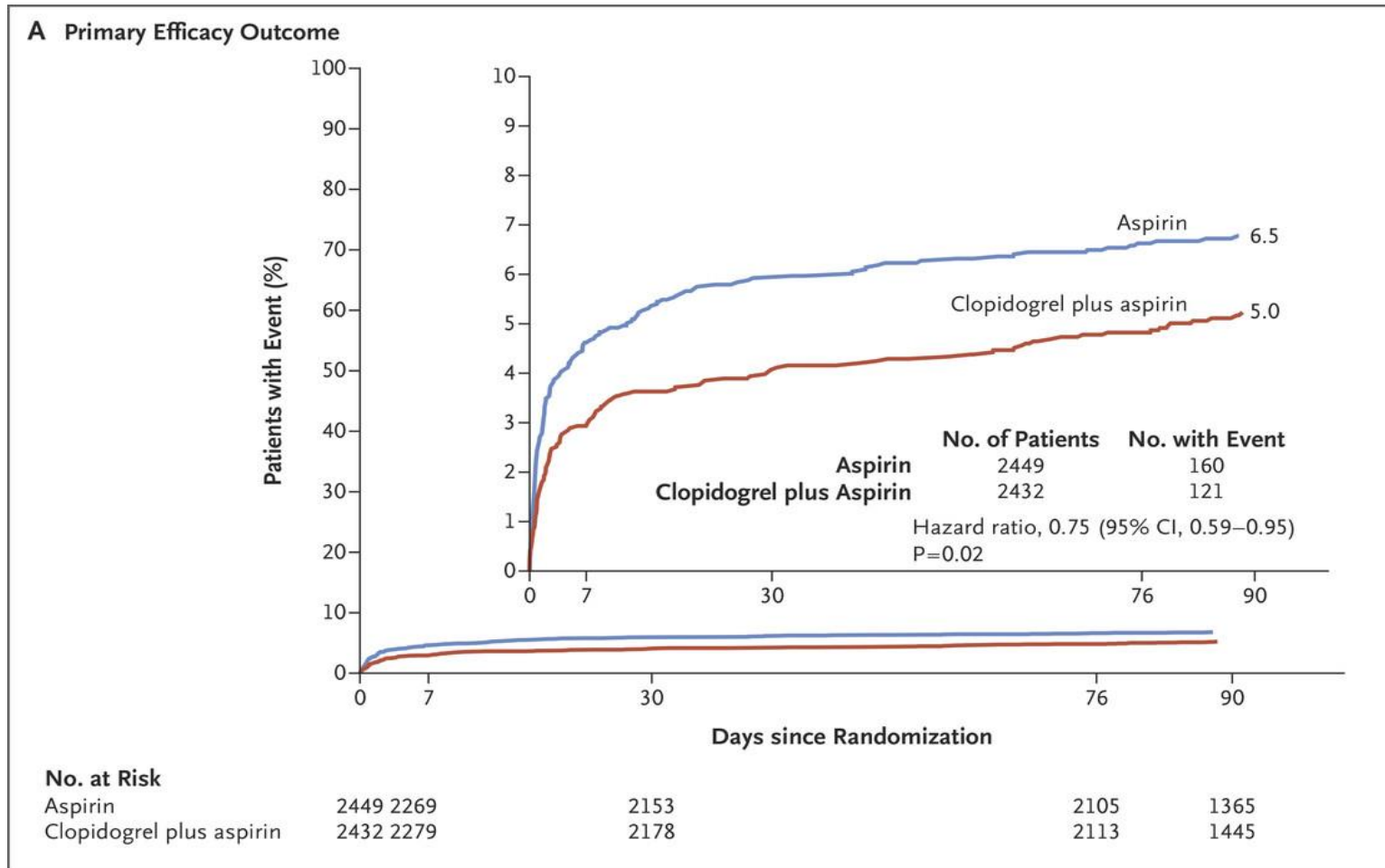
- 4,881 patients with minor AIS or high-risk TIA enrolled
 - Minor AIS – NIHSS ≤ 3
 - High-risk TIA – score of 4 or greater on ABCD

□ **Interventions:**

- A + C (2,432 patients)
 - Clopidogrel 600 mg X 1 then 75 mg/day for 90 days
 - Aspirin 50 – 325 mg/day for 90 days
- Aspirin (2,449 patients)
 - 50 – 325 mg/day for 90 days

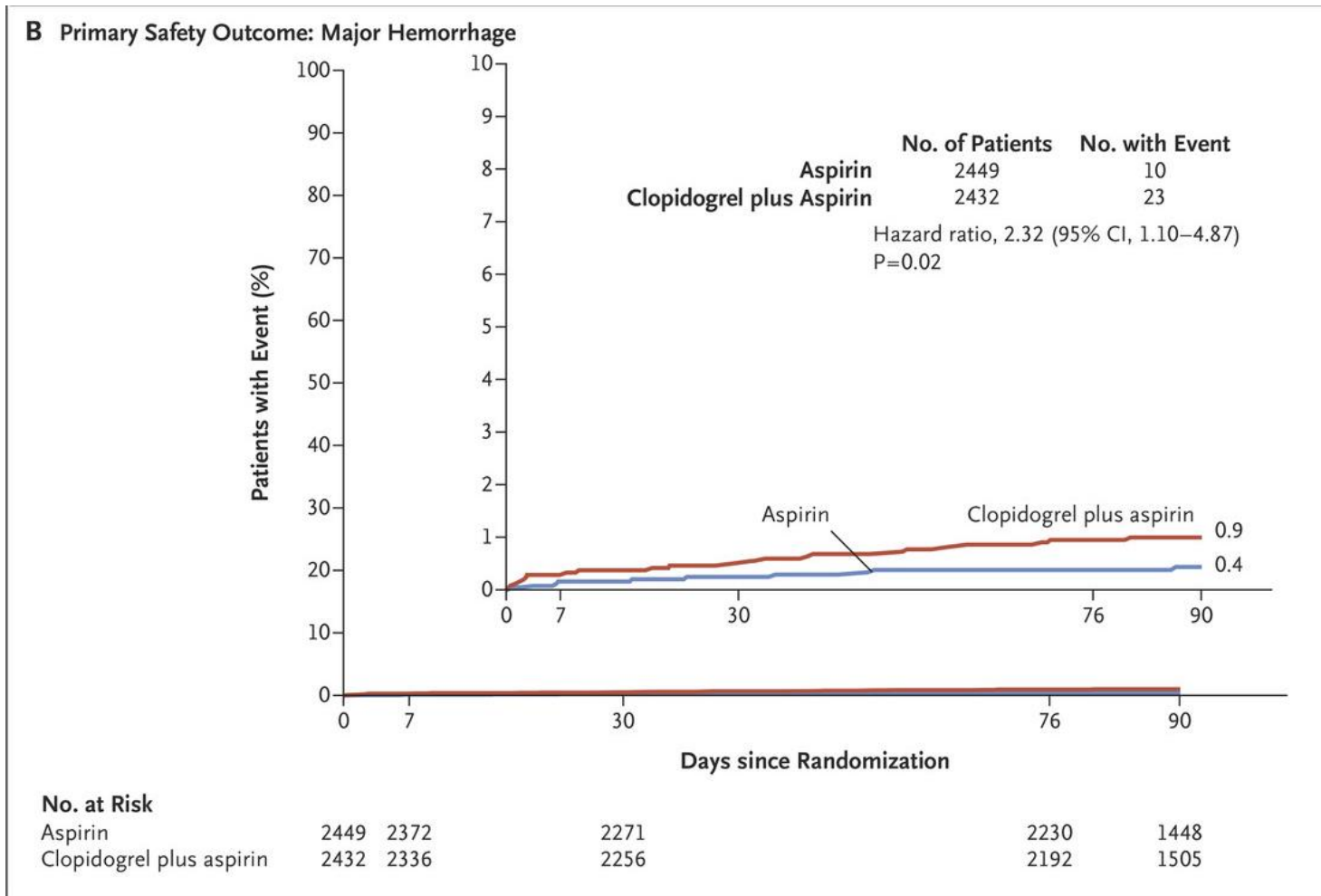
Point Trial Results: Primary Efficacy Outcome (Risk of Major Ischemic Event)

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Point Trial Results: Primary Safety Outcome (Major Hemorrhage)

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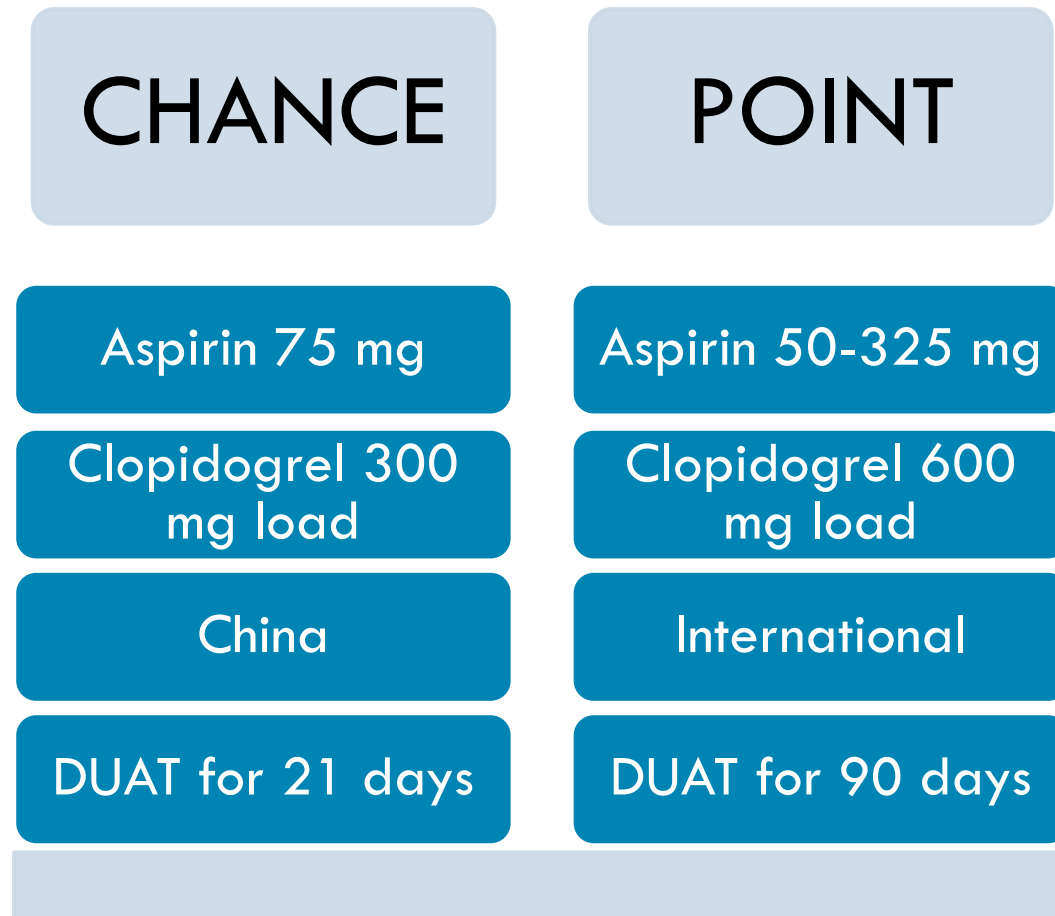
POINT Trial Conclusions

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- A+C vs. aspirin for minor AIS or high risk TIA resulted in...
 - ▣ Lower risk of major ischemic events at 90 days
 - ▣ Higher risk of major hemorrhage at 90 days
- Estimated benefit and harm per 1,000 patients treated with A + C:
 - ▣ 15 ischemic events prevents
 - ▣ 5 major hemorrhages caused
 - ▣ Could not compare disability outcomes
 - ▣ Most benefit observed in first month of trial

CHANCE vs. POINT Trials

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Clinical Implications of CHANCE and POINT Trials

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- DUAT may be beneficial for 21 days
- Excess hemorrhage may be observed with longer use
- Current guideline recommendations remain appropriate

Kate is a 54 year old female admitted to the hospital for a diagnosis of minor AIS (NIHSS score of 2). As the pharmacist on the unit you are asked whether Kate should be started on aspirin alone or aspirin + clopidogrel. Which of the following should you recommend based on the 2018 stroke guideline recommendations?

- A. Start aspirin alone since aspirin + clopidogrel should only be used in severe stroke.
- B. Aspirin + clopidogrel may be beneficial if used for up to 7 days.
- C. Aspirin + clopidogrel may be beneficial if used for up to 21 days.
- D. Aspirin + clopidogrel may be beneficial if used for up to 3 months.
- E. Aspirin + clopidogrel may be beneficial if used for up to 6 months.

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Anticoagulant Therapy in AIS

Guideline Recommendations

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Recommendation	COR	LOE
Urgent anticoagulation NOT recommended in AIS (unchanged recommendation)	III: No Benefit	A
Usefulness of urgent anticoagulation in patients with severe stenosis of an internal carotid artery ipsilateral to an ischemic stroke is not well established. (unchanged recommendation)	IIb	C-LD
Usefulness of thrombin inhibitors in AIS not well established (revised recommendation)	IIb	B-R
Usefulness of factor Xa inhibitors in AIS not well established (new recommendation)	IIb	C-LD

Summary

- NIHSS and noncontrast CT scan is recommended for initial patient evaluation
- IV alteplase is recommended for patients with AIS within 3-4.5 hours when no contraindications are present
- DTN < 45 – 60 minutes recommended when IV alteplase is used
- BP target of <185/110 and <180/105 mm Hg recommended pre- and post- alteplase therapy
- DUAT for 21 days may be beneficial in minor AIS
- Urgent anticoagulation not recommended after AIS
- Role of thrombin and factor Xa inhibitors for AIS not established

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